REMARKS

The Office Action and the cited and applied references have been carefully studied. No claim is allowed. Claims 1, 3-11, and 13-31 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

New claim 31 in Jepson format is added and is patentable for the same reasons discussed below for claims 1, 3-11 and 13-30.

Claims 1-5, 7-8, 10-13, 16-17, 20-21, 23, and 25-30 have been rejected for lack of written description under 35 U.S.C. 112, first paragraph because the examiner indicates that applicants' arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below. The examiner indicates that applicants argue that aside from the proteins disclosed in the specification, oligodeoxynucleotides (ODNs) were known in the art as adjuvants for stimulating immune responses and as such the skilled artisan would have recognized their usefulness in the instant invention. In support of this argument the applicant provides a post-filing publication demonstrating the inclusion of an ODN in HBsAg particles. While the applicant states that ODNs were known in the literature, the examiner holds that the literature did not report their use in vaccination in combination with HBsAg particles or disclose that ODNs could be encapsulated by

HBsAg particles. The examiner asserts that the specification is completely silent in regards to the characteristics of any ODN and provides no description or guidance for their inclusion in HBsAg particles. Further, Schirmbeck et al. (identified by the applicant as Reimann et al. on page 4 of the response received on 3/20/01) is said to be published after the filing of the instant application and teaches ODNs and methods of incorporating ODNs which were not known at the time of filing or taught by the specification. Thus, it is the examiner's position that the teachings of this article cannot be used to demonstrate the common knowledge of the skilled artisan prior to the filing of the instant application and therefore, the specification is held to not meet the written description provision of 35 U.S.C. 112, first paragraph, for biologically active molecules which are not proteins. This rejection is respectfully traversed.

The present specification discloses in the paragraph bridging pages 9 and 10 that immunostimulatory oligonucleotides containing certain palindromic sequences were found to induce IFN and augment the NK cell activity of mouse spleen cells, citing two Yamamoto et al. (1992 and 1994) references. In the same paragraph, the specification also teaches that other immunostimulatory oligonucleotides have been shown to be effective as adjuvants which induce the production of cytokines, activating B cells, monocytes, dendritic cells, and

NK cells, citing two references. Also attached hereto for the examiner's consideration are copies of two references, Carson et al., J. Exp. Med. 186(10)1621-1622 (1997) and Chu et al., J. Exp. Med. 186(10):1622-1631 (1997), which are representative of what was known in the art at the time the invention was made regarding the adjuvant Th1-promoting activity of ODNs for use in vaccines. It is clear that immunostimulatory ODNs were known to those of skill in the art as adjuvants.

The rejection of claims 1-30 under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained in part. The examiner indicates that applicants' arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

I. The examiner states that, as noted in the previous Office Action, the claims directed to compositions comprising the HBsAg particles containing a biologically active molecule are included in this rejection in terms of "how to use" the molecules according to the disclosure of the specification. In addition, the examiner notes that in regards to the methods of stimulating an immune response, the specification clearly teaches that the purpose of stimulating an immune response is for vaccination against infectious organisms such as viruses or bacteria (specification page 2). The specification does not provide any reason for stimulating

any immune response using the disclosed particles other than for protecting or treating infection.

The applicant argues that the term "encapsulation" encompasses both the noncovalent inclusion of a biologically active molecule in the interior of the particles or the exposure or presence of the molecule at the surface of the particle such that the molecule does not necessarily penetrate into the interior of the particle (applicant's response, page 6). In view of this definition of the term "encapsulation", it is acknowledged that the specification is enabling for making HBsAg particles which contain a hydrophobic protein or peptide, wherein the hydrophobic protein or peptide is incorporated into or attached to the HBsAg particle surface. It is noted by the examiner, however, that applicants have not presented any arguments or evidence refuting the lack of enablement for making HBsAg particles which contain non-covalent and non-chemically coupled hydrophobic proteins or peptides in the interior of the HBsAg particles. This part of the rejection is respectfully traversed.

The examiner's attention is respectfully directed to the specification at pages 5-6 where the structure of the HBsAg particles and their pores is discussed. The present specification teaches that phospholipids cover large areas of the outer and inner protein component of the particle and that the particle is hollow with access to the interior of the

particles being mediated by the presence of pores. Figures 2A and 2B show topographical images of HBsAg particles with the pores indicated by arrows. Clearly, proteins and peptides can be entrapped in the interior of HBsAg particles such as within the pores.

II. The examiner states that applicants argue that the specification provides sufficient guidance for routes and dosages of the instant particles and that several publications available in the art at the time of filing teach vaccination with HBsAg particles citing Bohm et al. (referred to as Reimann et al.), Ellis et al., Woodrow et al., and Ellis. However, the examiner holds that all of these publications are limited to the administration of unmodified HBsAg particles which do not contain a biologically active molecule according to the instant invention for the purpose of stimulating immune responses against the HBsAg antigen itself in order to vaccinate against hepatitis B. It is said that none of these references teach the level of non-HBsAg antigen concentration, dosage of non-HBsAg antigen containing HBsAg particles, or routes of modified particle delivery that result in the generation of enhancement of CTL or antibody responses against the incorporated non-HBsAg antigen, particularly in the circumstance where the non-HBsAg antigen by itself is ineffective in generating a CTL response. The examiner further notes that the unmodified HBsAg particles taught in the provided publications are clearly capable of

generating immune responses in the absence of any additional immunostimulatory molecule. Thus, while the provided publications demonstrate the induction of anti-HBsAg immune responses using unmodified HBsAg particles, the examiner holds that a nexus cannot be drawn between the use of the unmodified particles taught in these publications and the modified HBsAg particles disclosed in the specification. The examiner further states that the previous Office Action discussed in detail the parameters affecting the generation of different types of immune responses and the unpredictability of whether any level of any type of immune effector response against a particular antigen would correlate with a therapeutic effect on any disease associated with the immunizing antigen (Abbes et al., Golding et al., Yasumtomi et al., and Fox). While applicants are said to argue that the specification deals with the stimulation or modulation of MHC class I restricted CTL responses, it is the examiner's position that applicants' claims are broad and read on the stimulation or modification of any type of immune response (see claims 1, 5-11, and 14-16), and thus, the ability of the compositions to induce other types of immune responses besides a CTL response is a relevant issue to the enablement of the instant claims. This part of the rejection is respectfully traversed.

The claims are now amended to be directed to stimulating or modulating a CTL response and not to any type of immune response.

III. In regards to the encapsulation of cytokines, the examiner indicates that applicants argue that the specification discloses the successful use of IL-12 and IFN-gamma and that IL-2 may represent an inoperative species within the genus of immunostimulating molecules which would not preclude enablement for the broad claims. However, as discussed in the previous Office Action, the examiner holds that the genus of immunostimulating molecules is extremely broad and includes not only numerous cytokines with highly disparate functions, but also bacterial adjuvants and ODNs whose activity is unrelated to the activity of IL- 12 or IFN-gamma. Of the numerous species encompassed by the term immunostimulatory molecule, the examiner asserts that the specification does not provide sufficient guidance as to which cytokines, bacterial antigens, or ODNs would be capable of stimulating any type of immune response including a CTL response. It is pointed out by the examiner that the failure of IL-2 to stimulate a CTL response is important, as of the many known cytokines, IL-2 has been reported in the prior art to have CTL stimulating activity. Thus, the examiner takes the position that the applicants' demonstration that IL-2, a known CTL stimulating

cytokine, is ineffective in the instant particles and methods of stimulating CTL increases the unpredictability of determining what other cytokines, particularly those without known CTL stimulating activity, would be capable of achieving the desired result. The examiner indicates agreement with the district court's conclusion on enablement that, even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. This part of the rejection is respectfully traversed.

Applicants' initial lack of success with IL-2 as an immunostimulating molecule does not negate enablement. After the initial experiments were done and the present application was filed, applicants realized that the loading of HBsAg, which was conducted at 56°C, was simply conducted at too high a temperature for IL-2. While many protein are stable at 56°C, some proteins such as IL-2, do become inactivated. The fact that IL-2 loses its biological activity at such a temperature is taught in Kedar et al; "Delivery of cytokines by liposomes. I. Preparation and characterization of interleukin-2 encapsulated in long-circulating sterically stabilized liposomes", J. Immunother. 16:47-59 (1994), a copy of which will be submitted with a supplemental response.

IV. In regards to the immunization against HBV or HIV, the examiner indicates that applicants have provided

several publications which are reputed to provide a correlation between CTL generation and immunization with HIV or HBV antigens. These papers are said to demonstrate the induction of anti-HBV or anti-HIV specific CTL following a variety of different immunization strategies that are not related to the instant methods which involve the administration of modified HBsAg particles. The examiner states that the ability of HBV or HIV antigens to stimulate a CTL response in not at issue. The previous Office Action states that the specification does not provide an enabling disclosure for immunization against HBV or against diseases associated with antigen encapsulated by the HBsAg particles of the instant invention. The specification is said to disclose that the purpose of generating an immune response using the disclosed particles is for vaccination against disease, in particular HIV and HBV. However, it is the examiner's position that the specification does not provide any guidance or experimental data which correlates the observed level of CTL response generated against HIV/env/V3 in mice administered HIV/env/V3 encapsulated in HBsAg particles, or against HBsAg in mice administered HBsAg particles encapsulating IL-12, IFN, cholera toxin or enterotoxin, with any effect on HIV or HBV infection. The examiner holds that the art at the time of filing teaches that the strength and character of an immune response to a particular antigen or

epitope significantly affects the ability of the host to successfully protect against or ameliorate disease or infection (see Yasumtomi et al., and Fox). Thus, the examiner asserts that in view of the art recognized unpredictability of vaccinating against HIV, the lack of correlation between the applicants' CTL data and any effect on HIV or HBV infection, and the breadth of the claims, the skilled artisan would not have predicted success in vaccinating any mammal against any disease by administering HBsAg particles encapsulating a disease antigen and/or immunostimulatory molecule. This point the rejection is respectfully traversed.

Applicants submit that the claims as presently recited are now only directed to a method for stimulating or modulating a CTL response.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Claims 1, 5-6, 11, 17-18, 25-27, and 29-30 have been rejected under 35 U.S.C. 102(b) as being anticipated by Neurath (U.S. Patent No. 5,039,522). The examiner states that Neurath teaches that it is possible to add any peptide with a hydrophobic tail to HBsAg particles to produce an immunogen useful for generating immune responses against viral proteins or peptides (column 3, lines 39-51). Neurath is said to further teach that the peptide can be a naturally occurring or

synthetic peptide derived from HIV or hepatitis B (column 3, lines 46-62) and to teach the preparation of HBsAg particles which contain myristolated hepatitis B preS antigen by incubating myristoated preS protein with HBsAg in an aqueous media (column 10, lines 13-48). In addition, the examiner holds that Neurath teaches the immunization of rabbits with the preS containing HBsAg particles resulting in the generation of anti-HBV antibodies. The examiner notes that antigens are inherently considered immunostimulatory molecules as their expression results in the generation of immune responses and takes the position that by teaching all the limitations of the claims, Neurath anticipates the instant invention. This rejection is respectfully traversed.

Neurath discloses immunogenic peptides which have been modified with a covalently attached/linked hydrophobic tail (i.e., by myristilation as disclosed at column 9, lines 37055, and in the Examples) for adsorption to the surface of the HBsAg particle. By contrast, the antigenic molecule used in the presently claimed method is either entrapped within the interior of the particle or exposed or present at the surface of the particle. There is no covalent modification to the antigenic molecule, which includes a protein (e.g., ovalbumin as disclosed in the present specification) or peptide, as

supported by the specification on page 7, lines 24-25. Accordingly, Neurath cannot anticipate the present invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-2, 5-7, 11-12, 17-19, and 21 have been rejected under 35 U.S.C. 102(b) as being anticipated by Michel et al., Res. Virol. 144, 263-267 (1993). The examiner states that Michel teaches the production of HBsAg particles which incorporate a hybrid HIV env/V3 peptide in the exterior of the particles (page 264, column 2). The examiner notes that the HIV env/V3 peptide contains CTL epitopes as well as antibody and helper T cell epitopes and incudes an epitope capable of binding to murine Kd. Immunization of macaques with the hybrid HIV/HBsAg particles is said to result in anti-HIV and anti-HBsAg antibodies and CTL (page 266). It is the examiner's position that, by teaching all the elements of the claims, Michel anticipates the instant invention. This rejection is respectfully traversed.

Michel discloses hybrid recombinant HBsAg particles in which an antigenic molecule is cloned so that when expressed it is covalently linked to the HBsAg major protein as a fusion protein. By contrast, the antigenic molecule or biologically active molecule used in the present invention is not covalently linked to form fusion proteins as specifically taught in the

present specification on page 6, lines 18-20, and page 7, lines 12-15 and 24-25. Accordingly, Michel cannot anticipate the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 1, 3, 4, 10, 11, 13, 16, and 23 have been amended as follows:

1(Once-amended). A method of stimulating or modulating ~~an immune~~ a CTL response to an antigenic molecule in a mammalian subject, comprising administering to said subject an effective amount of a composition comprising ~~the~~ an antigenic molecule either entrapped within the interior of ~~contained in~~ an HBsAg particle or exposed or present at the surface of an HBsAg particle.

3(Once-amended). The method of claim ~~2~~ 1, wherein said CTL response is enhanced relative to that produced by the antigenic molecule alone.

4(Once-amended). The method of claim ~~2~~ 1, wherein said antigenic molecule, when administered without said HBsAg particle, is substantially ineffective in producing a CTL response in said subject.

10(Once-amended). The method of claim 8, wherein said immunostimulating molecule is an immunostimulatory oligonucleotide.

11(Once-amended). A method of stimulating or modulating ~~an immune~~ a CTL response to HBsAg in a mammalian subject, comprising administering to said subject an effective amount of a composition comprising an immunostimulating

molecule either entrapped within the interior of ~~contained in~~ an HBsAg particle or exposed or present at the surface of an HBsAg particle.

13(Once-amended). The method of claim ~~12~~ 11, wherein said subject is a nonresponder at the CTL level when administered HBsAg particles without said immunostimulating molecule.

16(Once-amended). The method of claim 11, wherein said immunostimulating molecule is an immunostimulatory oligonucleotide.

17(Once-amended). A composition comprising an HBsAg particle and a biologically active molecule either entrapped within the interior of an HBsAg particle or exposed or present at the surface of an HBsAg particle.

20(Once-amended). The composition of claim 17, further comprising an immunostimulating molecule either entrapped within the interior of said HBsAg particle or exposed or present at the surface of said HBsAg particle.

23(Once-amended). The composition of claim 21, wherein said immunostimulating molecule is an immunostimulatory oligonucleotide.